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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/716,095	11/18/2003	Alexandra Kaczmarek	21489	5755

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HOFFMANN-LA ROCHE INC.
PATENT LAW DEPARTMENT
340 KINGSLAND STREET
NUTLEY, NJ 07110

EXAMINER	
PARKIN, JEFFREY S	
ART UNIT	**PAPER NUMBER**
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/716,095	KACZMAREK ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Office Action

Status of the Claims

Acknowledgement is hereby made of receipt and entry of the communication filed 23 October, 2009. Claims 1-5 are pending in the instant application.

35 U.S.C. § 103(a)

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Oldenburg *et al*. (1994) in view of Lambert *et al*. (2000), Mukhopadhyay (1997), McCoy *et al*. (1991), and Vendenbark (1997). The claims are directed toward a process for the production of a recombinant antifusogenic peptide wherein said peptide is expressed as a repeat peptide in a microbial host. Expression of the repeat antifusogenic peptide leads to the formation of inclusion bodies. Additional steps encompassing washing the inclusion bodies with a denaturing agent (5.5 to 8.0 mol/l) at a pH at or below pH 6.5, solubilizing the washed

inclusion bodies at a pH value of at least pH 9 in the absence of detergents or denaturing agents, and cleaving the repeat peptide to obtain individual forms of the antifusogenic peptide. It was also stipulated that the peptide contains a glycine residue at the C-terminus. The most recent claim amendment specifies that the antifusogenic peptide comprises SEQ ID NO.: 2. This sequence corresponds to the known anti-HIV-1 fusion inhibitor DP-178 (also referred to as T-20).

As previously set forth, Oldenburg and colleagues disclose a recombinant parathyroid hormone analog, rPTH(1-34*), which was obtained from Escherichia coli using a gene polymerization strategy. The PTH gene polymer contains up to 8 copies of the gene, each separated by a cleavable linker. The polymer was expressed at very high levels and formed inclusion bodies which could be easily isolated by low-speed centrifugation. A polyhistidine leader peptide allows rapid purification via nickel chelation chromatography of the PTH polymer solubilized from the inclusion bodies. Yields of greater than 500 mg/liter have been obtained. After isolating the polymer, monomeric rPTH(1-34*) is released from the polymer by chemical cleavage with cyanogen bromide. Following cyanogen bromide cleavage and high-performance liquid chromatography purification, highly purified, biologically active rPTH(1-34*) is obtained at a yield of approximately 300 mg/liter. This teaching provides a general strategy for the high-level production of a variety of peptides and small proteins using cleavable repeat peptides and inclusion bodies. This teaching does not provide antifusogenic polypeptides with a C-terminal glycine or corresponding to DP-178/T-20.

Lambert and colleagues provide a number of antifusogenic peptides comprising DP178 (aa 638-673) (see Fig. 1; Summary of the Invention, cols. 3-5; Detailed Description of the Invention, cols. 12-16). These peptides are potent inhibitors of HIV-1 replication.

Mukhopadhyay (1997) provides a detailed review concerning the purification of proteins from inclusion bodies. Various formats are disclosed including the utilization of a denaturing agent at the recited range. Moreover, this teaching provides detailed formats for solubilizing inclusion bodies including the utilization of high pH buffers. The author also provided routine criteria to employ when assessing which solvent to employ (see last paragraph, p. 85).

McCoy and associates (1991) provide detailed methodologies for solubilizing inclusion bodies containing a biologically active polypeptide through the utilization of high pH buffers (see the claims and representative examples). The authors noted that high pH buffers were an economical means for solubilizing inclusion bodies. It was also noted that denaturing agents and detergents suffered from a number of limitations when attempting to produce large quantities of the soluble, active protein.

Finally, Vandenbark (1997) teaches the inclusion of C-terminal glycine residues in polypeptides is useful because it facilitates their conjugation to other carrier molecules or it facilitates their synthesis during solid-phase syntheses.

Therefore, it would have been *prima facie* obvious at the time of the invention to utilize the polypeptide inhibitors of Lambert *et al*. (2000), in the protocols of Oldenburg *et al*. (1994), since this would facilitate the high-level production of purified peptide. One of ordinary skill in the art would also be motivated to employ the purification protocols provided by Mukhopadhyay (1997) and McCoy *et al*. (1991), since this would also facilitate the high-level production of peptide. One of ordinary skill in the art would have been further motivated to incorporate a C-terminal Gly, as taught by Vandenbark (1997), to facilitate the synthesis of the fusion peptides or the conjugation to a carrier molecule.

Response to Arguments

Applicants traverse and submit that Oldenburg differs in at least four of the claimed elements which are not remedied by the additional references relied upon (see arguments set forth on page 4 of the response). Oldenburg and colleagues unequivocally demonstrate that tandem repeats of a biologically active polypeptide can be isolated and purified utilizing inclusion bodies. As previously set forth, this reference provides a general strategy for the high-level production of a variety of peptides and small proteins using inclusion bodies. The claimed elements allegedly lacking are clearly provided by the additional references relied upon.

Applicants argue that Oldenburg *et al*. (1994) teach away from the claimed invention because it requires metal chelation chromatography, cleavage of the peptide with CNBr, and a peptide with a homoserine/homoserine lactone residue at the carboxyl-terminus. This teaching is relied upon because it clearly

teaches the concept of expressing a repeat peptide in a microbial host using inclusion bodies. The carboxyl-terminal peptide modification results from the cleavage of the peptide using CN-Br. However, any number of art-recognized cleavage strategies could be employed (e.g., enzymatic cleavage sites (trypsin, chymotrypsin) could be added to the peptide of interest). Moreover, other modifications could be employed such as those disclosed by Vandenbark (1997). Thus teaching discloses the inclusion of C-terminal glycine residues in polypeptides is useful because it facilitates their conjugation to other carrier molecules or it facilitates their synthesis during solid-phase syntheses. Thus, one of ordinary skill in the art would have been motivated to modify the C-terminus of the DP-178 peptides of Barney et al. (2000) to include such a modification.

Additional arguments were provided suggesting that Mukhopadhyay (1997) also failed to address any of the deficiencies in Oldenburg. It was argued that this teaching fails to provide a washing step at a pH value below 6.5 in the presence of a denaturing agent followed by a solublization step at a pH>9.0. This argument is also incorrect. As previously set forth, this teaching provides a detailed analysis of routine inclusion body purification protocols, including the utilization denaturing agents at pH values below 6.5 and solubilizing agents comprising high pH buffers (see pages 83-87). The author also provided routine criteria to employ when assessing which solvent to employ (see last paragraph, p. 85). Thus, one of ordinary skill in the art need only select from a limited number of possibilities (e.g., GuHCL, SDS, and/or high pH) to ascertain the most suitable purification protocol.

It was also argued that Vandenbark (1997) fails to remedy any of the deficiencies of Oldenburg. Once again applicants' arguments are not tenable. Vandenbark clearly teaches the inclusion of C-terminal glycine residues in polypeptides is useful because it facilitates their conjugation to other carrier molecules or it facilitates their synthesis during solid-phase syntheses. Thus, one of ordinary skill in the art would have been motivated to modify the antifusogenic HIV-1 polypeptides of Lambert *et al*. (2000) to include a C-terminal glycine. This would obviously facilitate the conjugation of these molecules to other carrier proteins after purification.

Additional arguments stressed that Lambert *et al*. (2000) also fails to remedy any of the deficiencies in Oldenburg. Contrary to applicants' assertion, this teaching clearly provided a number of antifusogenic peptides comprising DP178 (aa 638-673) which are potent inhibitors of HIV-1 replication. Thus, this teaching clearly supplies an antifusogenic peptide as required by the claim language.

In summarizing their arguments, applicants submit that Oldenburg and colleagues teach away from the claimed invention because CNBr cleavage leads to the production of a polypeptide with homoserine/homoserine lactone residues at the terminus. This argument was addressed supra wherein it was noted that different methods of cleavage and peptide modification could be employed depending upon the cleavage system employed (e.g., chemical or proteolytic) and final peptide properties desired (e.g., addition of a label or carrier). Applicants are reminded

that the rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992). See also *In re Kotzab*, 217 F.3d 1365, 1370, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000) (setting forth test for implicit teachings); *In re Eli Lilly & Co.*, 902 F.2d 943, 14 U.S.P.Q.2d 1741 (Fed. Cir. 1990) (discussion of reliance on legal precedent); *In re Nilssen*, 851 F.2d 1401, 1403, 7 U.S.P.Q.2d 1500, 1502 (Fed. Cir. 1988) (references do not have to explicitly suggest combining teachings); *Ex parte Clapp*, 227 U.S.P.Q. 972 (Bd. Pat. App. & Inter. 1985) (examiner must present convincing line of reasoning supporting rejection); and *Ex parte Levengood*, 28 U.S.P.Q.2d 1300 (Bd. Pat. App. & Inter. 1993) (reliance on logic and sound scientific reasoning). Methods for the purification of biologically active proteins using inclusion bodies were well-known in the prior art. Various solubilization methods were also well-known in the prior art. In fact, applicants' own disclosure also states that purification methods employing inclusion bodies were well-known (see p. 15). The crux of the invention appears to be directed toward the "surprising" discovery that the claimed fusion proteins were capable of being purified using a high pH buffer. There is nothing surprising about this finding, particularly in view of the teachings of McCoy *et al*. (1991), who clearly demonstrate that biologically active proteins can be purified from inclusion bodies by solubilization at high pH.

Therefore, the claimed invention is clearly *prima facie* obvious in view of the teachings of the prior art.

Action Is Final

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 10:30 AM to 9:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Robert B. Mondesi, can be reached at (571) 272-0956. Direct general status inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Applicants are reminded that the United States Patent and Trademark Office (Office) requires most patent related correspondence to be: a) faxed to the Central FAX number (571-273-8300) (updated as of July 15, 2005), b) hand carried or delivered to the Customer Service Window (now located at the

Randolph Building, 401 Dulany Street, Alexandria, VA 22314), c) mailed to the mailing address set forth in 37 C.F.R. § 1.1 (e.g., P.O. Box 1450, Alexandria, VA 22313-1450), or d) transmitted to the Office using the Office's Electronic Filing System. This notice replaces all prior Office notices specifying a specific fax number or hand carry address for certain patent related correspondence. For further information refer to the Updated Notice of Centralized Delivery and Facsimile Transmission Policy for Patent Related Correspondence, and Exceptions Thereto, 1292 Off. Gaz. Pat. Office 186 (March 29, 2005).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

/Jeffrey S. Parkin/
Primary Examiner, Art Unit 1648

19 January, 2010